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Robert C. Ladner

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EXAMINER

BOESEN, CHRISTIAN C

ART UNIT

PAPER NUMBER

1636

NOTIFICATION DATE

DELIVERY MODE

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ELECTRONIC

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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<b>Office Action Summary</b>	<b>Application No.</b> 10/656,350	<b>Applicant(s)</b> LADNER ET AL.	
	<b>Examiner</b> CHRISTIAN BOESEN	<b>Art Unit</b> 1636	

**-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --**

### Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

### Status

- 1) ☒ Responsive to communication(s) filed on \_\_\_\_.
- 2a) ☐ This action is **FINAL**.                      2b) ☒ This action is non-final.
- 3) ☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on \_\_\_\_; the restriction requirement and election have been incorporated into this action.
- 4) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

### Disposition of Claims

- 5) ☒ Claim(s) 1-9,11-18,20-28,40,42 and 44 is/are pending in the application.
- 5a) Of the above claim(s) \_\_\_\_ is/are withdrawn from consideration.
- 6) ☐ Claim(s) \_\_\_\_ is/are allowed.
- 7) ☒ Claim(s) 1-9,11-18,20-28,40,42 and 44 is/are rejected.
- 8) ☐ Claim(s) \_\_\_\_ is/are objected to.
- 9) ☐ Claim(s) \_\_\_\_ are subject to restriction and/or election requirement.

### Application Papers

- 10) ☐ The specification is objected to by the Examiner.
- 11) ☐ The drawing(s) filed on \_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 12) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

### Priority under 35 U.S.C. § 119

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All    b) ☐ Some \*    c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
  2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_.
  3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- \* See the attached detailed Office action for a list of the certified copies not received.

### Attachment(s)

- |  |   |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892)                                | 4) <input type="checkbox"/> Interview Summary (PTO-413)<br>Paper No(s)/Mail Date. ____. |
| 2) <input type="checkbox"/> Notice of Draftperson's Patent Drawing Review (PTO-948)                        | 5) <input type="checkbox"/> Notice of Informal Patent Application                       |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)<br>Paper No(s)/Mail Date ____. | 6) <input type="checkbox"/> Other: ____.  |

### **DETAILED ACTION**

This Non-Final Office Action is responsive to the communication received 12/23/2010.

#### ***Continued Examination Under 37 CFR 1.114***

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 12/23/2010 has been entered.

#### ***Previous Rejections and/or Objections***

Any objections and/or rejections raised in the previous Office Action but not reiterated below are considered to have been withdrawn.

#### ***Claim Rejections - 35 USC § 112 (New Matter) - New***

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-9, 11-18 and 40 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the

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claimed invention. This is a new matter rejection. Claims 2-9, 11-18 and 40 depend directly or indirectly on claim 1.

Amended claim 1 states "e) producing replicate phage from the infected cells in the presence of the target immobilized to the support, thereby forming replicate phage immobilized to the support via binding to the target of step (a), wherein the producing is completed in less than 2 hours; f) separating replicate phage that do not bind to the target of step (a) from the replicate phage immobilized to the support".

Applicant cites page 8, lines 5-8 in the originally filed specification for support (corresponding to paragraph [0049] in the instant PG Publication) in the Reply filed 10/28/2008.

At this location the specification states "In one embodiment, the methods further include one or more of: during step iv), fewer than 5000, 4000, 2000, 1000, 700, 500, 300, or 100 progeny phage are produced for each phage that infects one of the host cells; step iv) is completed in less than 4, 3, 2, 1.5, 1, or 0.5 hours".

There is no connection between this embodiment and the current claimed embodiment which includes the limitation "of step (a)".

Applicant cites page 37, Example 2 in the originally filed specification for support (corresponding to paragraph [0239] to [0240] in the instant PG Publication) in the Reply filed 10/28/2008.

This disclosure is not commensurate in scope with the current claim. The disclosure contains a number of limitations such as, "a nickel chelating tag", "a phage display library that displays Fabs" and "nickel magnetic beads" that are not contained in the instant claim.

***Claim Rejections - 35 USC § 112 - 2nd paragraph***

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-9, 11-18 and 40 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claims 2-9, 11-18 and 40 depend directly or indirectly on claim 1.

Claim 1 is indefinite and unclear due to a lack of clear antecedent basis regarding the phrase “target immobilized to the support” in part b) of instant claim 1. There is no active immobilization method step in said part b), instead a past tense “immobilized” limitation. Note that previous in claim 1 there is only a target and a support cited in step a) but no antecedent therein that the target is actually immobilized to the support nor a method step directed to such immobilization.

***Claim Rejections - 35 USC § 103 - New***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

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The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. § 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.
5. Secondary considerations (objective evidence of nonobviousness): a) commercial success; b) long felt need; c) evidence of unexpected results; d) skepticism of experts; and e) copying.

*Common Ownership of Claimed Invention Presumed*

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the Examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the Examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-9, 12-13, 15-17, 20-28, 40, 42 and 44 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ladner et al. (04/04/1995) US Patent 5,403,484 (hereafter referred to as "Ladner") in view of Anderson (11/18/2003) US Patent 6,649,419 B1, Markland et al. (06/18/1996) Biochemistry volume 35 pages 8045 to 8057 (hereafter referred to as "Markland") and Kim et al. (11/01/1981) Proceedings of the National Academy of Sciences USA volume 71 pages 6784 to 6788 (hereafter referred to as "Kim").

Applicant's claimed invention is generally directed to a method for the ultra fast selection of antibodies from an antibody phage library. The Applicant's invention as set forth in claim 1 encompasses embodiments that are directed towards the use of phage display where selected phage are produced in 2 hours or less. The assay sets forth that each round of selection is completed in 8 hours or less using affinity filter screening of phage from a library using a target immobilized to solid substrate. The phage from the library that have affinity towards the immobilized target bind to the solid substrate through the target, while the unbound phage are removed/washed away. The target-bound phage are then used in the bound form to infect host cells, replicated, and screening is repeated using the same target-immobilized substrate.

Ladner is directed towards the identification of binding proteins using M13 bacteriophage display and rounds of selection and amplification.

As in part (a) of claim 1, Ladner teaches a method for screening a library of diverse phage (*i.e.*, KLMUT – a diverse library of over  $1 \times 10^5$  phage – col. 143, lines 57-60), each phage displaying heterologous protease inhibitors which are considered diverse protein

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components, such as EpiNE1 through EpiNE8 (col. 142, line 14 through col. 143, line 56) having binding affinity for a target (*i.e.*, human neutrophil elastase) immobilized to a solid substrate (*i.e.*, agarose beads) – see col. 144, lines 15-36. As in part (b) of claim 1, this section of Ladner teaches that the phage bind to the support through the target; as in part (c), phage that do not bind the target are eluted away (*i.e.*, separated); as in part (d), the particle-bound phage are infected into XL1-Blue™ cells (col. 144, lines 28-30); as in step (e), the previous infection reaction produced 348 plaques which were pooled for further affinity selection with the immobilized HNE-beads, and as in step (f) the non-binding phage are separated from the phage bound to the HNE-beads, and as in step (g), the host cells are contacted with these beads and infected with the phage to form a second population of cells.

As in claims 2 and 3, Ladner teaches recovering the second population of infected cells and recovering the phage from those cells (col. 144, lines 37-41).

Claim 4 is directed towards a third replication by repeating steps (e) through (g); Ladner teaches the third replicated series of steps (col. 144, lines 41-60).

As in claim 8, Ladner teaches adding an additional amount of target (*i.e.*, adding to an additional amount of a 50% slurry of beads - col. 144, lines 34-36).

As in claim 9, Ladner teaches use of the MB phage which is an M13 type phage (col. 118, lines 5-33) – Landner teaches that these phage typically produce between 100 and 1000 progeny (col. 55, lines 40-44), and therefore meet the limitations of the claim.

As in claim 13, Ladner teaches a diverse library of  $10^5$  phage with 97.4% of the approximately 97.4% possible DNA constructs – col. 143, lines 57-61.



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As in claim 15, the phage of the KLMUT library each have a gene that allows for replication in the host cell (see col. 55, lines 28-44; col. 118, lines 5-35; and col. 144, lines 18-36).

As in claim 16, Ladner teaches that the phage may be selected from a phagemid (col. 76, lines 39-40), and that the use of a helper phage can be carried out (col. 60, lines 44-46).

As in claim 17, Ladner teaches the use of competing ligands to enhance identifying phage with desired properties (col. 98, lines 43-49)

As in independent claim 20, Ladner teaches (a) providing a bacteriophage library that comprises a plurality of bacteriophage members - (*i.e.*, KLMUT – a diverse library of over  $1 \times 10^5$  phage – col. 143, lines 57-60;

(b) selecting a subset of the bacteriophage members – the step of binding the library of phage to the beads taught in Ladner; each phage displaying heterologous protease inhibitors which are considered diverse protein components, such as EpiNE1 through EpiNE8 (col. 142, line 14 through col. 143, line 56) having binding affinity for a target (*i.e.*, human neutrophil elastase) immobilized to a solid substrate (*i.e.*, agarose beads) – see col. 144, lines 15-36;

(c) infecting host cells with the members of the subset – Ladner teaches that the particle-bound phage are infected into XL1-Blue™ cells (col. 144, lines 28-30);

(d) amplifying members of the subset under at least one of the following conditions: (1) fewer than 5000 progeny phage are produced for each phage member selected in step (b) – Ladner teaches use of the MB phage which is an M13 type phage (col. 118, lines 5-33) – Ladner teaches that these phage typically produce between 100 and 1000 progeny (col. 55, lines 40-44);

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(e) selecting a subset of amplified members, thereby identifying the desired members of the bacteriophage library – Ladner teaches the affinity maturation process wherein the selected phage reintroduced to cells and propagate, which are further selected and propagated (*i.e.*, amplified), and identification of clones having the greatest affinity (col. 144, lines 37-61).

As in claim 21, the amplification process and selection process of Ladner occur in the presence of the target as the bead-bound phage infect the host cells and progeny are produced, wherein the progeny phage bind the target (col. 144, lines 37-61). As in claims 22 and 23, Ladner teaches that the target (which can be the cells binding to the solid support as defined by Applicants' specification – see specification page 0038) binds to the solid support during amplification; contacting the library to the target and solid support, wherein the bacteriophage library members bind to the target through the solid support (*i.e.*, beads) – see col. 144, lines 18-36.

As in independent claim 24, Ladner teaches a method for selecting a nucleic acid that encodes a binding protein comprising:

(a) providing a library of phage that each have a heterologous protein component that is diverse among the phage of the plurality, physically attached to the phage, and accessible – Ladner teaches a method for screening a library of diverse phage (*i.e.*, KLMUT – a diverse library of over  $1 \times 10^5$  phage – col. 143, lines 57-60), each phage displaying heterologous protease inhibitors which are considered diverse protein components, such as EpiNE1 through EpiNE8 (col. 142, line 14 through col. 143, line 56) having binding affinity for a target (*i.e.*, human neutrophil elastase) immobilized to a solid substrate (*i.e.*, agarose beads) – see col. 144, lines 15-36;

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(b) contacting phage of the library to a target – as noted above, Ladner teaches that the library of phage are introduced to the bead-immobilized target HNE;

(c) performing one or more cycles of:

i) forming phage immobilized to a support, each of which comprises (1) a phage that binds to the target by its heterologous protein component and (2) the target immobilized to a support – Ladner teaches that certain optimized heterologous proteins, such as EpiNE7.8 (col. 144, lines 50-61), bind to the immobilized HNE target,

ii) separating phage that do not bind to the target from the phage immobilized to the support via binding to the target – Ladner teaches that the phage that do not bind to the target are washed away, leaving behind phage that bind the target,

iii) contacting phage from the phage immobilized to the support with host cells so that the host cells are infected by the phage from the immobilized to the support – Ladner teaches that these phage that are bound to the target on the beads are used to infect the XL1-Blue™ cells (col. 144, lines 28-47), and

iv) producing phage from the infected cells in the presence of target, the produced phage being replicates of phage that bind to the target – Ladner teaches that the recovered phage are replicates of the initial phage, but comprise a smaller library greater affinity/selectivity towards the HNE target, such as EpiNE7.8 as noted above; and

(d) recovering the nucleic acid encoding the heterologous protein of one or more produced phage - Ladner teaches recovering the nucleic acid (col. 144, lines 47-61).

As in claim 25, the conditions of separating the phage vary in stringency – Ladner teaches varying the pH (col. 144, lines 26-28).

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As in claims 26 and 27, Ladner repeats the cycles of affinity maturation at least three times (col. 144, lines 15-61).

Although Ladner teaches performing his isolation of select phage bound to ligand-modified beads in reactions vessels, Ladner does not explicitly teach the use of the same target as carried out in step (a), such as a reusable target immobilized to a bead, nor the reduced production time of 2 hours. Ladner also does not explicitly teach that the reactions are carried out in the same vessel, such as the steps of (a) through (g), or the steps of (d) to (e) in claims 5 and 6, respectively; and although Ladner discloses the addition of further target immobilized to the bead (*i.e.*, HNE), Ladner does not explicitly suggest that the reaction can be performed without additional target, as in claim 7.

Anderson teaches a method for using magnetic beads to isolate biological components of interest, wherein the component of interest binds to a target that is attached to the bead. Anderson teaches that the reactions used with the beads can be used to recover the target, and further utilize the target component of interest by manipulating the bead that it is attached to, and does not require further addition of more target-immobilized beads:

“Once the protein is adsorbed to the beads, directly or via an affinity ligand, the composition is one of a denatured protein bound to the bead. The beads can be further manipulated by use of appropriate magnetic fields to perform processes such as digestion with protease, exposure to antibody mixtures in order to select those antibodies that specifically bind to the protein, and exposure to other proteins that may or may not be found to bind to the original protein.”

Anderson, col. 11, lines 29-37; and the beads can be reacted and maintained in a single reaction vessel:

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“Instead of moving the beads to other vessels, one may collect the beads and aspirate, wash and change the solution in the same vessel for performing the next step.”

Anderson, col. 29, lines 8-10.

Markland is directed towards the interactive optimization of high-affinity protease inhibitors using both traditional "slow" round of selection and a "quick" round of selection.

With regards to claim 28, Markland teaches each cycle is completed in less than 8 hours, for example, a "quick screen" round does not involve any phage production described in the "slow screen", thus each round includes 2 hrs of binding, a 30 sec microcentrifuge, five different 5 min washes and two different 5 min elutions (see Figure 3 and page 8048 left column lines 2 to 45).

Kim is directed towards identification of deletions in bacteriophage M13 that remain viable.

With regards to claims 1e, 12, 20d, 24aiv, 28, 40, 42 and 44, Kim teaches wild type bacteriophage M13 are produced exponentially from a starting concentration of  $10^8$  replicate and produces a concentration of  $10^{10}$  after 30 minutes,  $3 \times 10^{11}$  after 1 hr, at which time the production starts to level off to  $6 \times 10^{11}$  after 1.5 hrs,  $2 \times 10^{12}$  after 2 hrs and  $3 \times 10^{12}$  after 2.5 hrs (see Figure 5 and page 6786 right column line 9 to 19).

One of ordinary skill in the art at the time the invention was made would have had a reasonable expectation of success in arriving at the Applicant's invention as claimed with the above cited references before them. Ladner, Anderson, Markland and Kim are all directed

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towards methods using M13 bacteriophage. Ladner and Markland are all directed towards methods using M13 in phage display. Ladner, Anderson and Markland are all directed towards techniques that utilize beads/reaction supports for the isolation of biological components that have affinity for given ligands. One of ordinary skill in the art would have recognized the advantages of the single vessel approach used by Anderson in the phage targeting, isolation and growth as taught by Ladner, namely, the ease of use of having the selected biological component of interest contained to a single location that easily permits rapid addition and removal of reagents and reaction byproducts. Furthermore, one of ordinary skill in the art would have recognized the reusable nature of the beads as taught by Anderson, and recognized these advantages in the method of Ladner, such as reduced quantities of reagents.

Ladner and Markland both teach the traditional "slow" round of phage display selection and Markland compared the "slow" with a "quick" round of phage display selection. The disadvantage of the "slow" round is the need for overnight production of phage. Only a small percentage of the total phage produced overnight is used in the next day's round of selection. One of ordinary skill in the art would have recognized that the advantage of the "quick" round of phage display saves time, for example, three rounds of "slow" selection takes three days while three rounds of "quick" selection can be completed in one day. Markland teaches the advantage of the "slow" selection is an identical amount of input phage for each round while in the "quick" selection the amount of input phage for each round is reduced (see Markland, page 8048 left column lines 2 to 15). Kim teaches that an overnight incubation is not required for phage production because phage are produced exponentially after 30 minutes the production starts to level off after 1.5 hrs (see Kim, Figure 5 and page 6786 right column line 9 to 19). One of

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ordinary skill in the art would have recognized the advantages of shortening the overnight incubation to save time as well as having a production step between each round to increase the phage input for the subsequent round. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Claims 1-9, 11-18, 20-28, 40, 42 and 44 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ladner et al. (04/04/1995) US Patent 5,403,484 (hereafter referred to as "Ladner") in view of Anderson (11/18/2003) US Patent 6,649,419 B1, Markland et al. (06/18/1996) Biochemistry volume 35 pages 8045 to 8057 (hereafter referred to as "Markland"), Kim et al. (11/01/1981) Proceedings of the National Academy of Sciences USA volume 71 pages 6784 to 6788 (hereafter referred to as "Kim"), Steinbuchel et al. (02/08/2000) US Patent 6,022,729 (hereafter referred to as "Steinbuchel"), Janda (11/05/1996) US Patent 5,571,681 and McCafferty et al. (10/19/1999) US Patent 5,969,108 (hereafter referred to as "McCafferty").

The limitations of claims 1-9, 12-13, 15-17, 20-28, 40, 42 and 44, and the corresponding teachings in Ladner, Anderson, Markland and Kim are presented above, and are hereby incorporated into the instant rejection.

Although Ladner provides certain general guidelines and conditions for reaction times involving the phage, Ladner does not explicitly teach reaction times of less than 2 hours for step (e) or steps (d) and (f), as in claims 10 and 12, or the cycles being less than 8 hours as in claim 28; nor does Anderson. Ladner also does not explicitly teach a change in the temperature upon the producing step as in claim 14; nor does Anderson.

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Janda generally teaches the use of covalent conjugates that are immobilized by attachment to a substrate through a solid phase and are easily separated from unconjugated elements of the combinatorial library by stringent washing. Janda generally teaches combinatorial libraries employing phagemid-display are particularly preferred since such phagemids include genetic material for identifying and amplifying conjugated catalysts. In describing the reactions for contact phage with the host cell, incubating the cell, and expressing the phage in the host cell, the processes can be carried out in less than four hours, such as the 15 minutes to infect the XL1-Blue™ cells, and the 2 hour culturing – note that the overnight cell selection with kanamycin is not required due to the beads being able to select the phage of interest and only captures progeny phage produced from the first round of binding to the bead that produced in the host cell (col. 25, lines 37-50). As in claim 14, Janda teaches going from room temperature during infection to 37 degrees C during incubation (col. 25, lines 37-50).

One of ordinary skill in the art would have had a reasonable expectation of success in arriving at the invention as claimed because each of Ladner, Anderson and Janda are directed towards the use of methods for affinity selection of phage to a library of targets using bead-based strategies. Although Ladner does not explicitly recite the claimed time limitations or temperature change, such adjustments to those parameters are considered routine in the art, as exemplified by Janda, and are well within the purview of the ordinary artisan, especially considering that there is nothing in Applicants' disclosure that would present any objective indicia of non-obviousness (*e.g.*, there are no teachings of unexpected results based on the claimed limitations). Therefore, the invention as whole was *prima facie* obvious at the time it was invented.



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Although each of Ladner and Janda each teach the use of the host cells XL1-Blue™ cells for preparing a phage library, and Janda teaches certain reaction times and temperatures, neither teaches that the host cells divide less than seven times as in claim 11.

Steinbuchel is directed to the use of certain host cells, such as XL1-Blue™ cells, for producing mutant polypeptide strains, wherein the host cells have been transfected with various constructs, such as pSKC07 and pSK2665 (see col. 14, lines 27-55). Over the course of cell growth, Steinbuchel shows the growth rate of the XL1-Blue™ cells under standard conditions (see Figure 5). As can be seen from Figure 5, the time for the host cell population to double, or equivalently carry out one division on average, is between about 30 minutes (closed symbols) and less than four hours (open symbols)<sup>1</sup>.

One of ordinary skill in the art would have had a reasonable expectation of success in arriving at the invention as claimed because each of Ladner and Janda are directed towards the use of methods for affinity selection of phage to a library of targets using bead-based strategies, and Steinbuchel is directed towards the use of the same host cells for producing mutant polypeptides. Although Ladner does not explicitly recited the claimed time limitations or temperature change (nor Anderson), such adjustments to those parameters are considered routine in the art, as exemplified by Janda, or the growth rate of XL1-Blue™ cells within the time frame of Janda resulting in less than seven divisions, and are well within the purview of the ordinary artisan, especially considering that there is nothing in Applicants' disclosure that would present and objective indicia of non-obviousness (*e.g.*, there are no teachings of unexpected results based

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<sup>1</sup> The graph is plotted as optical density which equivalent to an absorbance measurement produced from the XL1-Blue™ cells, where  $A = abc$ ; (A, absorbance; a, molar absorptivity; b, path length, and c, concentration of host cells) – therefore, a doubling in the OD is a result of a doubling of the concentration/number of the host cells, or one cell division.

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on the claimed limitations). Therefore, the invention as whole was *prima facie* obvious at the time it was invented.

Although Ladner teaches the use of phage for producing a library of heterologous proteins with improved affinity, Ladner does not teach the use of mutator host strains as claimed in claim 18.

McCafferty teaches a member of a specific binding pair (sbp) is identified by expressing DNA encoding a genetically diverse population of such sbp members in recombinant host cells in which the sbp members are displayed in functional form at the surface of a secreted recombinant genetic display package (rgdp) containing DNA encoding the sbp member or a polypeptide component thereof, by virtue of the sbp member or a polypeptide component thereof being expressed as a fusion with a capsid component of the rgdp. The displayed sbps may be selected by affinity with a complementary sbp member, and the DNA recovered from selected rgdps for expression of the selected sbp members (see Abstract). McCafferty also uses subsequent rounds of selection and mutagenesis (col. 6, lines 1-5). Regarding mutagenesis, McCafferty teaches the value that mutator strains provide for combinatorial chemistry when using phage:

“It will often be necessary to increase the diversity of a population of genes cloned for the display of their proteins on phage or to mutate an individual nucleotide sequence. Although in vitro or in vivo mutagenesis techniques could be used for either purpose, a particularly suitable method would be to use mutator strains. A mutator strain is a strain which contains a genetic defect which causes DNA replicated within it to be mutated with respect to its parent DNA. Hence if a population of genes as gene III fusions is introduced into these strains it will be further diversified and can then be transferred to a non-mutator strain, if desired, for display and selection.”

McCafferty, col. 9, lines 50-61.

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One of ordinary skill in the art would have had a reasonable expectation of success in arriving at the invention as claimed because each of Ladner, Anderson, Chandrashekar and McCafferty are directed towards developing mutant heterologous polypeptides with phage display, wherein the selected phage have improved affinity/activity towards a given target. One of ordinary skill in the art would have been motivated to utilize a mutator strain as taught by McCafferty for the host cells of Ladner during the affinity maturation process because the mutator strains provide a convenient way to increase the diversity of genes used by the phage to display the library member. Therefore, the invention as a whole was *prima facie* obvious at the time it was invented.

#### Discussion and Answer to Argument

Applicant's arguments (Reply, page 9 line 5) are based on the amendment of "2 hours", Applicant is respectfully directed to the above new rejections for an answer to arguments.

#### **Conclusion**

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to CHRISTIAN BOESEN whose telephone number is 571-270-1321. The Examiner can normally be reached on Monday-Friday 9:00 AM to 5:00 PM.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Ardin Marschel can be reached on 571-272-0718. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300. Information

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regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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